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THE LOWER URINARY TRACT

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The bladder and urethra are concerned with the collection and storage of urine, the voiding of this urine at consciously chosen times once continence has been acquired and the ability to prevent leakage between these times.

To achieve these functions the structure and response of the bladder and urethra must be normal and this requires the absence of local urinary tract disease, the presence of an intact nerve supply and (in females) a satisfactory hormonal environment. When these conditions are met the following physiological functions can occur:

1. Distension of the bladder.
2. Normal sensation of bladder filling.
3. Voluntary inhibition of bladder emptying.
4. Voluntary initiation of bladder emptying.
5. Co-ordinated inter-action between bladder and urethra during filling phase and voiding phase.
6. Normal urethral closure.

Anatomy and innervation of bladder and urethra

Recent work by Gosling (1979) has clarified the anatomy of the human bladder and urethra and their innervation. The nerve supply of the detrusor is predominantly parasympathetic with a sparse supply of sympathetic noradrenergic nerves. In the male the bladder neck has a rich supply of noradrenergic nerves and a sparse parasympathetic cholinergic innervation, whereas in the female the reverse is true. The striated muscle (slow twitch) which constitutes

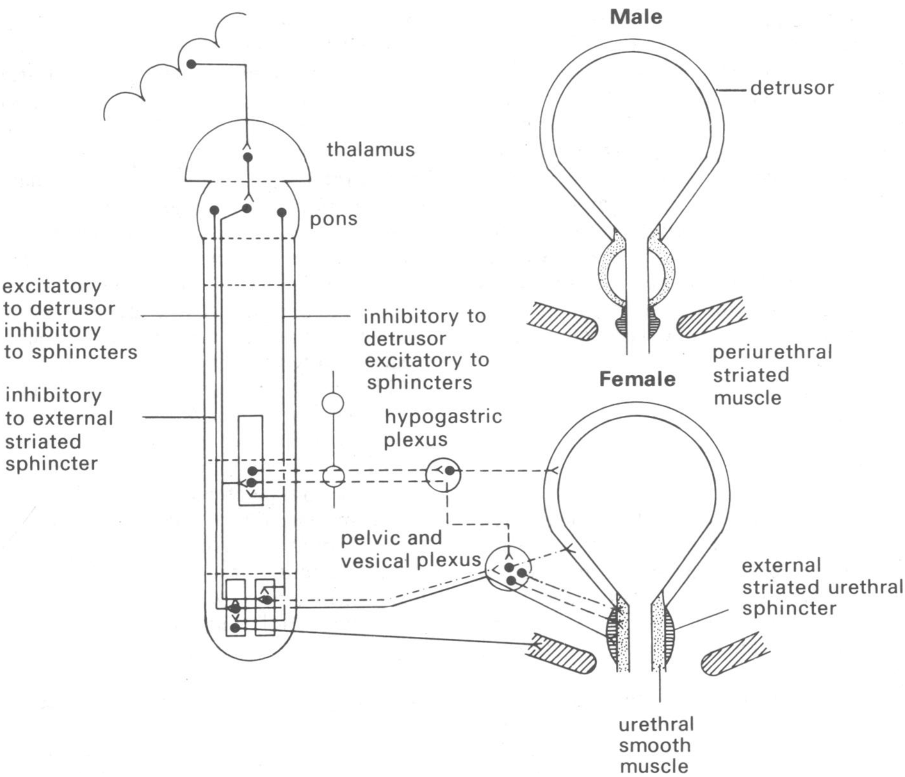

Figure 1 Innervation of bladder and urethra with diagrammatic representation of central nervous pathways (Fletcher & Bradley, 1978). Sympathetic pathways (----) synapse chiefly in the hypogastric plexus and parasympathetic (-.-.-.-) in the pelvic/vesical plexus. The striated sphincters are innervated by somatic (———) nerves.

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the external urethral sphincter is supplied by somatic fibres travelling via the pelvic plexus; the periurethral striated muscle (fast twitch) is supplied by somatic fibres via the pudendal nerve (Figure 1).

Visceral afferent fibres from bladder and urethra and somatic afferents travelling via the pudendal nerve synapse in the posterior grey horn. Afferent fibres are involved via interneurones in spinal reflex arcs with sympathetic, parasympathetic and somatic efferent pathways.

Normal micturition requires afferent input to nuclei in the brain stem, particularly those of the pons, via projection neurones which ascend from the synapses in the posterior grey horn. Descending fibres emerge from the brain stem in three tracts. The principal pathway which is a component of the lateral reticulospinal tract produces sustained excitation of the preganglionic neurones to the detrusor along with inhibition of neurones to the smooth and striated urethral sphincters. Another pathway descends in the medial reticulospinal tract and inhibits neurones of the external (striated) urethral sphincter. Impulses passing along these pathways facilitate micturition. The third pathway descends in the ventral reticulospinal tract; it inhibits detrusor neurones and excites sphincter neurones for continence. Decussation of afferent fibres and of efferent fibres takes place both in the cord and in the brain.

Some afferent projection neurones (and other sensory fibres) ascend to relay in the thalamus where there is conscious perception of bladder and urethral sensations, including bladder fullness and pain and urethral touch and tension. Above the brain stem a cortical detrusor muscle area is located in the superomedial portion of the frontal lobe. Fibres ascending to and descending from this area via the thalamus (the principal cerebral relay centre) pass through the internal capsule. The basal ganglia, limbic system, hypothalamus and cerebellum may also influence micturition.

Terminology and definitions

The literature on lower urinary tract function is often difficult to interpret because of failure to define terms particularly in the area of neurogenic dysfunction where several systems of classification have been described (Wein, 1981). The International Continence Society Committee for Standardization of Terminology has published a series of reports in which terms are defined. It is hoped that adoption of this terminology will facilitate comparison of results obtained by investigators using urodynamic methods. The Committee recommends that acknowledgements of these standards should be made in publications by a footnote to the effect that 'methods, definitions and units conform to the standards proposed by the International Continence Society except where specifically noted'. Their first report deals with urinary incontinence, the evaluation of urine storage (cystometry and urethral closure pressure profile) and units of measurement (Bates *et al.*, 1977a). The second report covers the evaluation of micturition (flow and pressure measurement during voiding) and gives a list of symbols for use in urodynamics (Bates *et al.*, 1977b). The third report deals with pressure-flow relationships and residual urine (Bates *et al.*, 1978). The fourth report contains recommendations related to neuromuscular dysfunction with particular reference to classification of the neuropathic bladder (International Continence Society Committee on Standardization of Terminology, 1981).

A series of guidelines is given below to assist understanding of published work in this field. This is based on the review of classifications by Wein (1981), the ICS recommended terminology and descriptions of urodynamic methods (Bates & Corney, 1971; Torrens & Abrams, 1979; Warwick, 1979).

An *uninhibited detrusor contraction* (the hallmark of an unstable detrusor) is an intrinsic bladder pressure rise exceeding 15 cm water occurring either spontaneously or with provocation, for example by passive posture change or cough, during a filling cystometrogram when the patient has been asked to inhibit bladder contraction; this may be a phasic contraction or simply a pressure elevation. It is necessary to establish that a pressure rise recorded via a catheter in the bladder is 'intrinsic', i.e. is caused by contraction or low compliance of the bladder rather than an increase in intra-abdominal pressure; to this end extravesical pressure must be measured. This is usually done via a catheter in the rectum. The intra-abdominal pressure is then subtracted from the measured bladder pressure to give the pressure generated by the bladder itself. Sophisticated recording equipment will do this electronically to give a separate tracing of intrinsic bladder pressure (Figure 2: Bates, 1971).

The terms *unstable detrusor* and *detrusor dyssynergia*, which are synonymous, simply denote the occurrence of these uninhibited contractions and do not imply any specific underlying disorder. However, the term *uninhibited neurogenic bladder* indicates that uninhibited detrusor contractions are occurring as a result of disturbance of the neurological control mechanisms; *detrusor hyper-reflexia* also denotes this abnormality and usually implies that the bladder contractions occur spontaneously, rather than on provocation, during the cystometrogram. A *reflex bladder* also exhibits uninhibited contractions; its owner is unable to perceive bladder filling whereas the person with an uninhibited neurogenic bladder retains perception of bladder filling.

The normal pattern in voluntary voiding is for urethral relaxation to begin just prior to detrusor

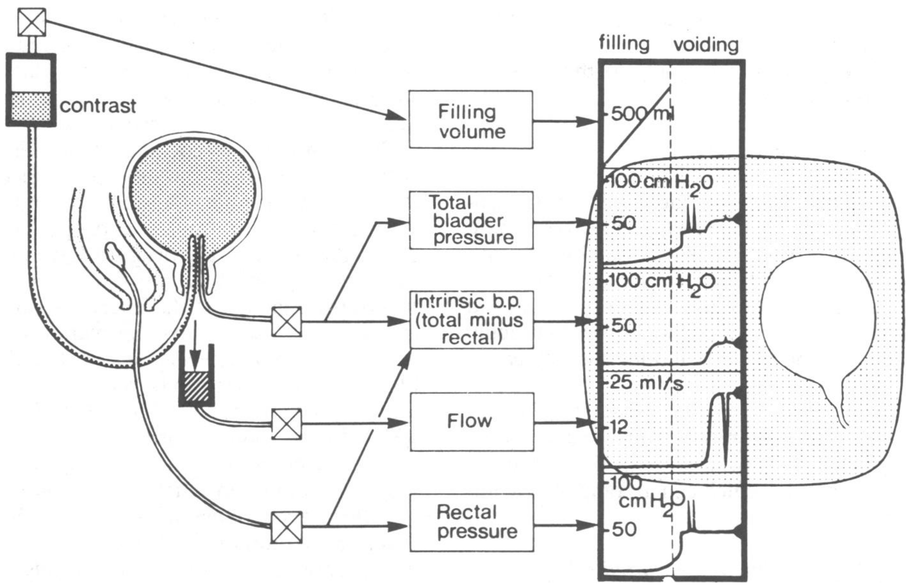

Figure 2 Synchronous pressure/flow cystourethrography: diagrammatic representation of apparatus. The record of intrinsic bladder pressure is obtained by subtracting the rectal from the total bladder pressure electrically. (Bates, 1971). Reproduced by permission of author and publisher.

contraction and for the urethra to remain relaxed until the detrusor contraction dies away having effected complete bladder emptying. This satisfactory co-ordination of detrusor and urethral sphincters may also occur when voiding results from an uninhibited detrusor contraction. However, during voluntary or involuntary voiding either one or both urethral sphincters may contract rather than relax. This is described as *detrusor-striated sphincter dyssynergia* or *detrusor-smooth muscle sphincter dyssynergia*. Both may occur together. A further variation, in combination with either a normal voiding contraction or an uninhibited contraction, is *non-relaxation of the smooth muscle sphincter* (rather than contraction) *during a bladder contraction*.

Rather than being over-active the detrusor may remain stable during filling but be unable to initiate a voiding contraction; this is a *non-contractile detrusor*. If the inability to contract exists because of abnormalities of neurological control the term *detrusor areflexia* may be used. This disorder may be associated with one of several types of urethral sphincter activity. Co-ordinated urethral sphincter activity may occur in that the sphincters relax when bladder emptying is desired. There may be non-relaxation of either the striated or the smooth muscle sphincter, causing incomplete bladder emptying; or the striated sphincter may be denervated, and therefore flaccid, in which case leakage of urine is likely to occur. An areflexic bladder may have normal sensation of filling if only the motor limb of the sacral micturition reflex arc is defective (the *motor paralytic bladder*); in this instance no voluntary detrusor contraction can be generated nor do uninhibited contractions occur.

The *sensory paralytic bladder*, in which the sensory limb of the sacral reflex arc or the ascending sensory tracts are damaged, is areflexic when no voiding contractions can be produced or hyporeflexic when only poor voiding contractions can be produced. An areflexic bladder will also develop if there is both motor and sensory separation of the bladder from the sacral spinal cord. This may be caused by damage to the sacral roots, the pelvic splanchnic nerves or the sacral spinal cord itself; this type of bladder is also referred to as *autonomous*. Patients with an autonomous bladder have no sensation of bladder filling, are unable to generate voluntary detrusor contractions and have no uninhibited contractions although small autonomous waves may be seen on cystometrogram.

It is clearly very easy to cause confusion by the inaccurate use of terms. When it is necessary to use a term not defined in the ICS reports it is essential that a statement of its precise meaning is made.

Drug effects on bladder and urethra

Drugs may influence the lower urinary tract by acting either *directly* on the mucosa of the bladder and urethra, the muscle of the bladder, urethra and periurethral region and the elastic tissue of the urethra, or *indirectly* through the nerve supply to these tissues and the periurethral blood vessels.

Mucosa of bladder and urethra

Flavoxate is reported to have local anaesthetic properties (Pedersen *et al.*, 1973) which may contribute to its action in the relief of spasm caused by infection or mechanical irritation (Delaere *et al.*, 1977). Local application of cocaine to the mucosa of isolated innervated guinea pig bladder blocks the contractile response to pelvic nerve stimulation (Bissada *et al.*, 1979b).

Oestrogens can relieve urgency and dysuria concurrently with the restoration of normal vaginal mucosa (Salmon *et al.*, 1941); it seems likely that the urethritis and trigonitis which can accompany vaginitis account for these symptoms.

Muscle of bladder, urethra and periurethral region

Disorders affecting these muscles tend to make them contract either too much or too little. The usual manifestation of *increased detrusor muscle activity* is the occurrence of detrusor contractions at times other than during voluntary voiding. The detrusor instability occurs when insufficient inhibitory influence is exerted by supraspinal centres on the sacral micturition reflex arc. Instability is normal for infants because the higher centres have not matured; if present in later life it may be due to failure of brain maturation, unsatisfactory voluntary training of the bladder or a disorder of the central nervous system for example multiple sclerosis.

Drugs with direct relaxant effect on the bladder muscle might be expected to favourably influence the unstable bladder. Flavoxate has been shown to inhibit the activity of bladder muscle *in vitro* and to significantly increase capacity when given orally to patients with 'spastic bladder' (Setnikar *et al.*, 1960). By contrast Briggs *et al.* (1980) found no effect on bladder capacity or the volume at which detrusor instability developed when flavoxate was given intravenously or orally. Similarly oral administration made no improvement in the incontinence which accompanied this instability.

Prostaglandin synthetase inhibitors diminish detrusor activity. Measurement of the relaxation phase of cat detrusor strips to which one isometric stretch was applied showed that indomethacin treated strips relaxed more quickly than controls (Abdel-Rahman *et al.*, 1981). Flurbiprofen given to women with idiopathic detrusor instability reduced the number with urge incontinence and lessened the detrusor pressure rise seen during bladder filling but did not significantly reduce the number who developed uninhibited detrusor contractions (Cardozo *et al.*, 1980).

Dicyclomine produces smooth muscle relaxation directly and also blocks muscarinic cholinoceptors; it has been shown to increase bladder capacity, to suppress uninhibited detrusor contractions and to delay the urge to void (Fischer *et al.*, 1978).

Parasympathetic blocking drugs which act principally at muscarinic cholinoceptors include propantheline and atropine. Uninhibited contractions were suppressed by intra-muscular propantheline (Blaivas *et al.*, 1980); when the drug was given orally to their patients one third regained continence and their bladders remained stable. There appears to be also an atropine-resistant motor innervation to the bladder; in most animal species an electrically stimulated bladder contraction can be only partially inhibited by atropine (Ambache & Zar, 1970; Sjöstrand *et al.*, 1972). In this context Burnstock (1972) has postulated purinergic nerves releasing ATP as transmitter.

Emepronium, although having some anti-muscarinic effect, acts principally at nicotinic cholinoceptors. It suppresses uninhibited detrusor contractions when given intra-muscularly but not orally (Ritch *et al.*, 1977).

Tricyclic antidepressants are weak antagonists at muscarinic cholinoceptors (Sigg, 1959). They may also have some direct smooth muscle relaxant effects (Bissada *et al.*,1979a). Detrusor relaxation is mediated through β-adrenoceptors and Lipshultz *et al.* (1973) have shown that imipramine enhances β-sympathomimetic amine-induced relaxation in dog detrusor strips.

Histamine H_1-receptor blockade will diminish histamine provoked contraction of human isolated bladder dome muscle but H_2-receptor blockade has no effect (Khanna *et al.*, 1977).

Reduced detrusor muscle activity impairs bladder emptying. Drugs with direct simulant effect on the bladder muscle may be useful in such situations. Abrams & Feneley (1976) found that prostaglandins E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ produced slow contraction of human bladder muscle strips which was not influenced by neurotransmitter antagonists and thus seemed to represent a direct effect on the muscle; $F_{2\alpha}$ was the most potent. Kondo *et al.* (1980) showed that a derivative of $PGF_{2\alpha}$ by intravenous injection produced an increase in intrinsic bladder pressure. The effect was greater in patients with neurogenic bladder than in those with no disease relevant to the urinary tract. The majority of the former had spinal cord lesions and autonomous bladder. This suggests that if the sacral micturition reflex arc has been damaged there is increased sensitivity to prostaglandin. By contrast Bultitude *et al.* (1976) who studied the effects of intravesical PGE_2 in female patients with chronic urinary retention found that satisfactory detrusor contractions and voiding could be achieved with reduction of residual volume in the majority, who were without neurological disease. In those with neurological disease however the prostaglandin was ineffective.

Parasympathomimetic drugs with direct action on muscarinic cholinoceptors have been used to stimulate detrusor contraction. Bethanechol for example acts principally on the muscarinic cholinoceptors but also has minor nicotinic effects (Draper & Zorgniotti, 1954). Finkbeiner *et al.* (1977) reported that bethanechol increased the amplitude and frequency of contractile activity of dog isolated detrusor strips. However, Wein *et al.* (1980a) in a study of normal women and women with increased residual urine volume (without neurological disease or bladder outlet obstruction) found no change in residual urine or urine peak flow rate after bethanechol. There was nevertheless an increase in bladder pressure both at 100 ml and at maximum capacity. In another study he examined women with voiding dysfunction and significant residual urine (with neurological disease) and again found increase in bladder pressure at maximum capacity but no significant change either in residual volume or urine flow rate (Wein *et al.*, 1980b).

Compared with bethanechol, carbachol has much greater nicotinic activity. It will induce dose-related contraction of human bladder muscle strips (Bultitude *et al.*, 1976). Reports on its effectiveness *in vivo* are presented by Finkbeiner *et al.* (1977); some state that it will reduce bladder capacity, increase vesical tone and pressure, initiate desire to void at low bladder volume and produce a normal volume of residual urine. Another report indicates that only one of four spinal cord injury patients to whom carbachol was administered actually voided and this patient still had a large residual volume.

Cholinesterase inhibitors have similar effects to directly acting cholinomimetics. Neostigmine stimulated bladder contraction in patients with neurogenic bladder (Lapides *et al.*, 1958). Distigmine which has a longer duration of action caused rhythmic bladder contractions but did not stimulate voiding in patients with recent spinal cord injury (Smith *et al.*, 1974).

α-Adrenoceptor blockade with phenoxybenzamine can increase bladder capacity in patients with autonomous bladders perhaps because these bladders respond abnormally to sympathetic activity (Norlén & Sundin, 1978).

Over-activity of urethral and/or periurethral muscle will cause obstruction to outflow from the bladder. The proximal urethra of females is innervated mainly by cholinergic nerves but in males this region (the pre-prostatic urethra) has a predominantly noradrenergic innervation (Goslin *et al.*, 1977). However Ek (1978) reported a sparse supply of adrenergic nerves throughout the urethra in both sexes.

Despite the autonomic innervation emepronium given intramuscularly has not been shown to have any effect on maximum urethral pressure, functional urethral length or shape of the urethral pressure profile in women with urge incontinence but no neurological disorder (Ulmsten & Andersson, 1977).

Kaneko *et al.* (1980) studying males with long standing dysuria and low flow rate found in almost half that flow rate improved after α-adrenoceptor blockade with intravenous phentolamine; these workers also demonstrated by fluorescent histochemistry the presence of noradrenergic innervation in the bladder neck smooth muscle of both responders and non-responders. The increase in urethral pressure which has been observed on postural change (lying to sitting) in males with peripherally denervated bladders can be abolished by phentolamine (Parsons & Turton, 1980).

Dantrolene, by direct depressant action on skeletal muscle, can decrease outlet resistance at the level of the external sphincter (Bissada *et al.*, 1979b) as can baclofen (Hachen & Krucker, 1977).

Reduced activity of the urethral and peri-urethral muscle diminishes resistance to outflow from the bladder. Drugs can increase the activity of the smooth internal urethral sphincter. Phenylpropanolamine, an α-adrenoceptor agonist has been shown in a study of women with stress incontinence to improve maximum urethral closure pressure (with the bladder empty) by more than 20% (Montague & Stewart, 1979). Phenylpropanolamine also greatly improved the symptoms of stress incontinence (Awad *et al.*, 1978); in patients responding to the drug maximum urethral closure pressure was significantly increased when measured with the bladder empty but not when the bladder was full. Studies on smooth muscle preparations obtained from human urethra indicate that also present are β-adrenoceptors which mediate relaxation (Ek *et al.*, 1977). Gleason *et al.* (1974) showed that stress incontinence can resolve with β-adrenoceptor blockade by propranolol. No drugs have been shown to increase resistance to outflow by action on the striated muscle of the periurethral region; however, the intrinsic striated muscle of the male urethra has been demonstrated to have an adrenergic nerve supply and may therefore be amenable to pharmacological manipulation (Koyanagi, 1980).

Elastic tissue of the urethra

Brown (1977) suggests that oestrogen lack may impair function of this elastic tissue. It is known that in the dog at least the elastic tissue contributes to urethral wall tension (Downie & Awad, 1976).

Peri-urethral blood vessels

In the female dog it has been shown by measuring the urethral pressure profile before and after clamping the blood supply to the urethra that the vascular component accounts for one third of the resting intra-urethral closure pressure (Raz *et al.*, 1972).

This is not a comprehensive list of drugs which may influence the lower urinary tract; however, those drugs which have been most extensively used for this purpose have been described. It is important to appreciate that many drugs prescribed for conditions not related to the bladder and urethra may also affect the functioning of these organs.

Measurement of drug effects on bladder and urethra

The effects of drugs may be established by assessment of various characteristics before and after administration. The possible measures of drug response include histological appearance, the *in vitro* behaviour of isolated tissue, the *in vivo* physiological functions of bladder and urethra (collection and storage of urine and voluntary voiding) and symptoms present because of structural and/or functional abnormalities of the bladder and urethra.

The methods used to assess these characteristics are now outlined.

1. *Histological appearance*

The oestrogen-dependent mucosa of the vaginal wall, urethra and trigone of the bladder may be examined by taking a smear from the vaginal wall or urethra or obtaining cells from bladder washings. Microscopic appearance will indicate whether or not the cells have been deprived of oestrogen and methods are available for quantitating the oestrogen response by the appearance of the cells before and after oestrogen treatment. All the methods are based on the maturing effect of oestrogen and they comprise the maturation, eosinophilic and karyopyknotic indices, the former being the most commonly used.

Maturation index The maturation index (Frost, 1974) represents a differential count of the squamous cell population and is expressed as a percentage. At least two counts of 100 cells are made in representative fields (using a $\times 40$ objective) and the percentages of parabasal, intermediate and superficial cells are recorded; it is customary to record the percentage of parabasal cells on the left since they are the least mature and the superficial squames as the most mature on the right. An increase in parabasal cells is sometimes referred to as a 'shift to the left' and an increase in superficial squames as a 'shift to the right'. Butler & Taylor (1973) identify 4 types of cell for the maturation index; parabasal, small intermediate, large intermediate and superficial. From these figures they derive a maturation value by multiplying the percentage of each type of cell by a weighting factor (Meisels, 1967) and summing the products (maturation value = parabasal $\times$ 0.0 + small intermediate $\times$ 0.5 + large intermediate $\times$ 0.6 + superficial $\times$ 1.0).

Eosinophilic index This index (Wachtel, 1969) is derived from a simple count of the number of pink-staining squames per 100 cells and is based on the assumption that only mature cells take up the eosin.

Karyopyknotic (superficial cell) index The karyopyknotic index (Wachtel, 1969) establishes the percentage of cells with pyknotic nuclei (superficial cells) the parabasal cells being omitted from the count. At least 200 unselected superficial and intermediate squamous cells are counted and those with pyknotic nuclei are expressed as a percentage of the total.

These indices may be unreliable under certain circumstances which include recent intercourse (less than 48 h before taking the smear), the use of chemical pessaries or vaginal douches, inflammation of vagina or cervix uteri, uterine prolapse, leukoplakia, presence of other sex hormones, prolonged administration of high doses of oestrogen, liver disease and digitalis medication.

2. In vitro *responses of isolated tissues*

Contraction and relaxation of strips from bladder or urethra or of isolated, innervated bladder and/or urethra can be measured by isotonic and isometric methods; thus, response to drugs in various concentrations can be established. The methods are similar to those described earlier in this series for renal pelvis and ureter (Longrigg, 1982).

3. In vivo *measurements of collection, storage and voiding of urine*

The function of the intact lower urinary tract can be quantitated by a variety of urodynamic measurements.

Maximum cystometric capacity: a low capacity suggests a fibrotic indistensible bladder, a hypersensitive bladder or an unstable bladder.

Volume at first desire to void: if desire to void occurs with a very small volume in the bladder this suggests irritation within the bladder, for example atrophic trigonitis, cystitis, calculus or tumour; or an unstable bladder.

Absence/presence of uninhibited detrusor contractions and voluntary initiation of voiding: a normal bladder contracts when voiding is consciously desired and not at any other time.

Co-ordinated interaction between bladder and urethra during filling and voiding phases: during filling the detrusor muscle should be relaxed and the urethra closed; at the beginning of voiding the urethra should relax and then the detrusor contract; the urethra must remain relaxed throughout voiding and the detrusor contraction must be maintained until the bladder is completely empty.

Normal urethral closure: the closure mechanisms must be sufficient to keep the bladder neck closed at all times except during voiding; they must also allow for voluntary interruption of the urine stream during voiding.

Techniques are available to obtain each of these measurements. Table 1 lists these and the information they give.

Table 1 Techniques available for the quantitation of lower urinary tract function

Technique	*Information obtainable*
Catheterisation Auscultatory percussion (Guarino, 1981) Ultrasound (Holmes, 1967) Electronic differentiation of integrated bladder filling volume and micturition volume (Jonas *et al.*, 1979) ^{131}I labelled diodrast (Mulrow *et al.*, 1961) Radiography (Beer, 1936) Phenosulphthalein (Cotran & Kass, 1958) ^{131}I hippuran (Shand *et al.*, 1968)	Residual urine volume
Isotonic bladder volume registration (Sundin *et al.*, 1977)	Residual urine volume Maximum cystometric capacity
Simple cystometry (transurethral approach): liquid filling (Brown, 1973) Simple cystometry (Suprapubic approach): liquid filling (Jonas & Hohenfellner, 1978) Simple cystometry: gas filling (Merrill *et al.*, 1971)	Residual urine volume Volume at first desire to void Absence/presence of bladder pressure rise on filling. (In supine, sitting, erect positions) Maximum cystometric capacity Bladder pressure rise to void
Two channel cystometry: liquid filling (Brown, 1973) Two channel cystometry: gas filling (Warwick, 1979)	As for simple cystometry + discrimination between bladder pressure rise due to increase in intra-abdominal pressure or detrusor muscle abnormality (indistensibility, uninhibited contraction)
Synchronous pressure flow cystourethrography (Bates, 1971; Bates & Corney, 1971) (Figure 2)	As for two channel cystometry + electronic subtraction of intra-abdominal pressure from bladder pressure to give separate record of pressure generated by detrusor + electronic record of volume instilled into bladder + electronic record of voiding flow rate + X-ray appearance of bladder and urethra
Bladder pressure measurement by pressure-sensitive capsule and recording by telemetry (Warrell *et al.*, 1963) Bladder pressure measurement by urethral catheter and recording by telemetry (Thüroff *et al.*, 1980)	Bladder pressure measurement whilst mobile
Urethral closure pressure profile Side hole perfusion catheter (single lumen): liquid perfusion (Brown & Wickham, 1969) Side hole perfusion catheter (single lumen): gas perfusion (Tscholl & Lenzi, 1977)	Bladder pressure and subsequently pressures along urethra

Technique	Information
Side hole perfusion catheter (double lumen): liquid perfusion (Glen & Rowan, 1973) Liquid filled balloon catheter (double lumen): bladder pressure measured by open tip (Enhörning, 1961) Membrane catheter (four lumen): bladder pressure measured by open tip (Tanagho & Jonas, 1977) Microtransducer catheter (two lumen) (Tanagho, 1979)	Bladder pressure and simultaneously pressures along urethra
Simultaneous electronic (liquid) urethrocystometry ± microtransducer record intra-abdominal pressure (Ulmsten *et al.*, 1977)	Simultaneous record of bladder and intraurethral pressure ± intra-abdominal pressure
Static cystourethrogram (Drutz *et al.*, 1978) Chain cystourethrogram (Veatch, 1980)	Appearance of posterior urethro-vesical angle
Pelvic floor electromyography (EMG): anal electrode (Thomas, 1979) Pelvic floor EMG: vaginal electrode (Thomas, 1979)	Pelvic floor striated muscle activity
Urethral sphincter EMG (Thomas, 1979)	Urethral sphincter striated muscle activity
Bladder EMG (Boyce, 1952)	Bladder detrusor muscle activity
Liquid cystometrogram and EMG (Klugo & Cerny, 1978) Gas cystometrogram with EMG (Andersen *et al.*, 1978)	Correlation of detrusor contraction with striated muscle activity
Liquid urethral closure pressure profile with EMG (McGuire, 1977) Gas urethral closure pressure profile with EMG (Andersen & Bradley, 1976)	Correlation of urethral closure pressure with striated muscle activity
Combined pressure-flow, EMG and X-ray studies (Madesbacher, 1977)	As for synchronous pressure flow cystourethrography + anal and urethral sphincter striated muscle activity
Detrusor and urethral electromyelography (Bradley *et al.*, 1976)	Anatomic integrity of nerve supply detrusor muscle and urethra
Gas cystometrogram with electroencephalogram (EEG) (Bradley, 1977)	Correlation of detrusor contraction with cerebral activity
Uroflowmetry (Gleason *et al.*, 1976)	Maximum and average rate of urine flow

4. *Assessment of symptoms*

Increased frequency of micturition and incontinence are commonly encountered and are the symptoms which will be considered.

Frequency. Charting. A record of the frequency of voiding is kept by the patient or an attendant. It must be completed for 24 h periods and if comparisons are to be made before and after drug treatments other factors which may alter frequency of micturition, notably fluid intake, must be kept constant.

Incontinence: how often? Charting. A record is kept of the time of occurrence of incontinence, again for 24 h periods (Brocklehurst, 1967). This is most likely to be useful if relatively large volumes are lost at infrequent intervals (i.e. hourly or less often). It is tedious to record leakage occurring more frequently, as may be the case in a patient with stress induced incontinence which occurs on standing, walking and coughing; in this case it is unlikely that an accurate record will be achieved. With stress incontinence in particular, the amounts leaked can be very small and not recorded by the patient. This is especially so if on other occasions the leakage is substantial.

The patient herself may be unable to record the times of incontinence either because she has sensory impairment and is unaware that leakage has occurred or because she has mental impairment. Under these circumstances an attendant must chart the incontinence. This involves the attendant going to the patient at regular intervals, say hourly or two hourly, and noting if incontinence has occurred.

These methods of charting are particularly applicable to the daytime and are unlikely to be accurate during the night. The patient keeping her own record may wet the bed in her sleep and be unaware how frequently this has occurred during one night. If an attendant is completing the chart it may not be possible for him/her to check the patient for incontinence as frequently as during the day. A 'pad and bell' method may be used to establish when incontinence occurs during the night. This type of device uses the electrolytes of urine to complete an electrical circuit by bridging the gap between two metal/foil pads. This activates a bell (Turner, 1973) or a timer (Ely Science Systems Ltd, 3 Longfields, Ely, Cambridgeshire, CB6 3DN).

Incontinence: how much? Charting. When recording the frequency of incontinence the patient (or attendant) may indicate the approximate amount of leakage for example 'few drops', 'moderate amount' or 'large amount'; alternatively 'damp' or 'soaked'.

Pad changes. The number of pads used each day may give an indication of frequency of occurrence or amount of incontinence (or both). Since the tolerance to dampness of pad varies greatly between individuals this method can only be used to assess changes in incontinence for an individual patient.

Pad weighing (dry and wet) can give an indication of the volume leaked (Sutherst *et al.*, 1981; Walsh & Mills, 1981). The latter authors point out that this method will be accurate only if the pads are worn with close fitting elasticated net pants which keep them snugly in position and prevent leakage. Their study of healthy volunteers showed that weight gain of pads due to perspiration was minimal and that weight loss resulting from evaporation was also negligible.

The Urilos Nappy (James *et al.*, 1971; Wilson *et al.*, 1980) is a disposable paper pad which contains dry electrolyte and supports aluminium strip electrodes. Urine is absorbed into the nappy, the change in the nappy's electrical capacitance is measured by an attached monitor and the equivalent urine volume (ml) is displayed on a calibrated meter. The Urilos system can measure volumes up to 100 ml only.

These urodynamic and symptomatic measures of lower urinary tract dysfunction may be used to assess the effects of drug treatment administered in an attempt to correct the underlying abnormalities. The disturbances of function encountered can be any of the following, alone or in combination.

1. Lack of bladder distention.
2. Increase or decrease in sensation of bladder filling.
3. Impairment of inhibition of bladder emptying.
4. Impairment of initiation of bladder emptying.
5. Inco-ordination between bladder and urethra during filling and/or voiding phase.
6. Increase or decrease in urethral closure pressure.

Abnormalities 1 to 4 may be demonstrated urodynamically by two channel cystometry and the influence of relevant drugs could be assessed by this method (Table 1).

Abnormality 6 may be shown by urethral closure pressure profile. Pressure within the urethra can be measured by a single lumen catheter withdrawn through the urethra; however, the important value is the urethral closure pressure and therefore it is most useful to simultaneously measure bladder pressure with urethral pressure. This requires a double lumen catheter.

Abnormality 5 can be demonstrated only if pressure in the bladder and urethra are measured at the same time (simultaneous urethrocystometry). To establish whether urethral pressure increase is due to contraction of smooth or striated muscle, electromyography must also be carried out concurrently. The urethral sphincter EMG indicates activity in the striated component of the sphincter and the pelvic floor EMG indicates activity in the periurethral striated muscle.

Influence of a model drug: emepronium

Effects of drugs on bladder and urethra vary according to the route of administration, whether oral, parenteral, intravesical or transcutaneous. Parenteral emepronium for example can abolish uninhibited detrusor contractions (Ritch *et al.*, 1977; Cardozo & Stanton, 1979) but given orally it has been shown to have less (Hebjørn & Walter, 1978) or even no effect (Ritch *et al.*, 1977) on detrusor contraction. Intravesical administration of emepronium produced no significant change in bladder pressure or capacity (Öbrink & Bunne, 1978). A transcutaneous preparation of emepronium is not available but the more lipid soluble hyoscine has recently been produced in the form of a skin patch for testing on bladder function (Ciba-Geigy).

There is considerable variation in the serum or plasma concentration maximum achieved with a particular dose of emepronium given orally, intramuscularly or intravesically. From those few studies in which drug concentration and urodynamic response have been recorded it would seem that a peak serum concentration in excess of about 30 μg/l is required for there to be effects on the cystometrogram (Table 2).

It is important when studying drug effects to compare active preparation with placebo. In a double blind cross over study comparing the combination of emepronium and flavoxate with placebo, it was found that 7 of 14 patients who initially had unstable bladders were stable on the active drugs but 4 were stable on placebo also (Brocklehurst & Robinson, unpublished).

Similarly it is necessary to distinguish between the effects of drugs and the effects of training. In urge incontinence associated with detrusor instability bladder training has proved the most effective treatment. At the end of three months, 41 of 50 women were continent, free of all urinary symptoms and had normal cystometrograms (Frewen, 1979). The training regime involved informing the patients of the nature and aetiology of their symptoms and the methods by which it was proposed to overcome them; the aim was to increase bladder capacity day by day and prolong the intervals between voiding. The first 7 to 10 days of treatment was carried out in hospital and during this time the patient kept a chart of frequency of voiding and occurrence of leakage (with amount). Nortriptyline was prescribed during the period of treatment with either emepronium or propantheline, all by mouth. Although the charting was carried out only for the in-patient period of management, the patients were instructed to continue increasing the intervals between micturition after discharge until a 4-hourly pattern was achieved. These results are more satisfactory than those reported in other drug trials. A tricyclic antidepressant alone achieved continence in only 3 of 9 patients (Cole & Fried, 1972). Emepronium alone cured only 2 of 17 incontinent patients with detrusor instability (Jönsson & Zederfeldt, 1957). Propantheline was given intramuscularly to 42 incontinent patients with detrusor instability: in 33 the instability was abolished or occurred after filling with at least twice the volume held at the initial cystometogram; 25 of these positive responders were treated with oral propantheline and only 8 became continent. By contrast biofeedback bladder training without drugs enabled 11 of 27 patients with unstable bladder to regain continence (Cardozo *et al.*, 1978).

Conclusions

Adequate assessment of drug effects on bladder and urethra requires that when a drug is given by an acceptable route its activity can be demonstrated by urodynamic measurement and symptom relief. This activity must be present in the absence of unaccept-

Table 2 Influence of emepronium on bladder function: plasma/serum concentration* and urodynamic response**

Dose	*Route*	*Concentration* ($\mu g/l$)	*Bladder capacity*	*Volume before leakage*	*Pressure during voiding*	*Urine flow rate*	*Residual volume*	*Authors*
0.3 mg/kg	i.m.	450	–	–	↓	↓	↑	Boman & von Garrelts (1973)
25 mg	i.m.	677	↑	↑	–	–	↑	Ulmsten & Andersson (1977)
300 mg	oral	36–64	↑	↑	–	–	O	
300 mg/day	oral	35	O	O	–	–	–	Hebjørn & Walter (1978)
600 mg/day	oral	76	↑	↑	–	–	O	
≤100 mg	intravesical	< 25	O	–	–	–	↑	Öbrink & Bunne (1978)

* peak value (individual, mean or range)
** ↑ increase, ↓ decrease, O no change, – not measured

able side-effects and must be shown to be superior to placebo or to retraining methods in the absence of drugs.

Few studies have fulfilled these criteria in a homogenous group of patients. It is very difficult, especially amongst the elderly, to find patients with only one abnormality responsible for their incontinence or those with a number of concurrent abnormalities which remain unchanged whilst one disorder is treated.

Perhaps if studies on drugs influencing the bladder and urethra are more carefully evaluated, for instance by correlation of symptomatic relief, urodynamic effect and serum/plasma drug concentration then the use of drugs in the management of urinary incontinence will become more effective.

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References

ABDEL-RAHMAN, M., COULOMBE, A. & ELHILALI, M.M. (1981). Detrusor dynamics II. Effect of prostaglandins and their synthesis inhibitor in stress–relaxation time course. *Invest. Urol.*, **18**, 281–284.

ABRAMS, P.H. & FENELEY, R.C.L. (1976). The actions of prostaglandins on smooth muscle of the human urinary tract *in vitro*. *Br. J. Urol.*, **47**, 909–915.

AMBACHE, N. & ZAR, M.A. (1970). Non-cholinergic nature of the postganglionic motor neurones in guinea-pig bladder. *J. Physiol.*, **209**, 10–12.

ANDERSEN, J.T. & BRADLEY, W.E. (1976). The urethral closure pressure profile. A new technique using gas and simultaneous EMG recording from the urethra. *Br. J. Urol.*, **48**, 341–345.

ANDERSEN, J.T., NORDLING, J. & WALTER, S. (1978). Gas cystometry and sphincter electromyography in assessment of urinary incontinence in the female. *Clin. Obstet. Gynecol.*, **21**, 679–693.

AWAD, S.A., DOWNIE, J.W. & KIRULUTA, H.G. (1978). Alpha-adrenergic agents in urinary disorders of the proximal urethra. *Br. J. Urol.*, **50**, 332–335.

BATES, C.P. (1971). Continence and incontinence. A clinical study of the dynamics of voiding and of the sphincter mechanism. *Annals of the Royal College of Surgeons of England*, **49**, 18–35.

BATES, P., BRADLEY, W.E., GLEN, E., GRIFFITHS, D., MELCHIOR, H., ROWAN, D., STERLING, A. & HALD, T. (The International Continence Society Committee on Standardisation of Terminology). (1978). Third report on the standardisation of terminology of lower urinary tract function. *Scand. J. Urol. Nephrol.*, **12**, 191–193.

BATES, P., BRADLEY, W.E., GLEN, E., MELCHIOR, H., ROWAN, D., STERLING, A. & HALD, T. (The International Continence Society Committee on Standardisation of Terminology). (1977a). First report on the standardisation of terminology of lower urinary tract function. *Scand. J. Urol. Nephrol.*, **11**, 193–196.

BATES, C.P. & CORNEY, C.E. (1971). Synchronous cine-pressure-flow cystography: a method of routine urodynamic investigation. *Br. J. Radiol.*, **44**, 44–50.

BATES, P., GLEN, E., GRIFFITHS, D., MELCHIOR, H., ROWAN, D., STERLING, A., ZINNER, N. & HALD, T. (The International Continence Society Committee on Standardisation of Terminology). (1977b). Second report on the standardisation of terminology of lower urinary tract function. *Scand. J. Urol. Nephrol.*, **11**, 197–199.

BEER, E. (1936). Visualisation of the amount of residual urine. *J. Am. med. Ass.*, **107**, 1886.

BISSADA, N.K., FINKBEINER, A.E. & WELCH, L.T. (1979a). Uropharmacology: X. Central nervous system stimulants and depressants. *Urology*, **13**, 464–473.

BISSADA, N.K., FINKBEINER, A.E. & WELCH, L.T. (1979b). Uropharmacology: XII. Miscellaneous drugs affecting lower urinary tract. *Urology*, **14**, 309–316.

BLAIVAS, J.G., LABIB, K.B., MICHALIK, S.J. & ZAYED, A.A.H. (1980). Cystometric response to propantheline in detrusor hyper-reflexia: therapeutic implications. *J. Urol.*, **124**, 259–262.

BOMAN, J. & von GARRELTS, B. (1973). Emepronium bromide—the effect on bladder pressure and urinary flow in healthy subjects. *Scand. J. Urol. Nephrol.*, **7**, 153–157.

BOYCE, W.H. (1952). Bladder electromyography: a new approach to the diagnosis of urinary bladder dysfunction. *J. Urol.*, **67**, 650–658.

BRADLEY, W.E. (1977). Electroencephalography and bladder innervation. *J. Urol.*, **118**, 412–414.

BRADLEY, W.E., ROCKSWOLD, G.L., TIMM, G.W. & SCOTT, F.B. (1976). Neurology of micturition. *J. Urol.*, **115**, 481–486.

BRIGGS, R.S., CASTLEDEN, C.M. & ASHER, M.J. (1980). The effect of flavoxate on uninhibited detrusor contractions and urinary incontinence in the elderly. *J. Urol.*, **123**, 665–666.

BROCKLEHURST, J.C. (1967). The treatment of incontinence. *Gerontologia Clinica*, **9**, 298–309.

BROWN, M. (1973). Cystometry. *Br. J. hosp. Med.*, (Equipment supplement), **10**, 33–41.

BROWN, A.D. (1977). Postmenopausal urinary problems. *Clin. Obstet. Gynaecol.*, **4**, 181–206.

BROWN, M. & WICKHAM, J.E.A. (1969). The urethral pressure profile. *Br. J. Urol.*, **41**, 211–217.

BULTITUDE, M.I., HILLS, N.H. & SHUTTLEWORTH, K.E.D. (1976). Clinical and experimental studies on the action of prostaglandins and their synthesis inhibitors on detrusor muscle *in vitro* and *in vivo*. *Br. J. Urol.*, **48**, 631–637.

BURNSTOCK, G. (1972). Purinergic nerves. *Pharmac. Rev.*, **24**, 509–581.

BUTLER, E.B. & TAYLOR, D.S. (1973). The postnatal smear. *Acta Cytologica*, **17**, 237–240.

CARDOZO, L.D., ABRAMS, P.D., STANTON, S.L. & FENELEY, R.C.L. (1978). Idiopathic detrusor instability treated by biofeedback. *Br. J. Urol.*, **50**, 521–523.

CARDOZO, L.D. & STANTON, S.L. (1979). An objective comparison of the effects of parenterally administered drugs in patients suffering from detrusor instability. *J. Urol.*, **122**, 58–59.

CARDOZO, L.D., STANTON, S.L., ROBINSON, H. & HOLE, E. (1980). Evaluation of flurbiprofen in detrusor instability. *Br. med. J.*, **280**, 281–282.

COLE, A.T. & FRIED, F.A. (1972). Favourable experiences with imipramine in the treatment of neurogenic bladder. *J. Urol.*, **107**, 44–45.

COTRAN, R.S. & KASS, E.H. (1958). Determination of the volume of residual urine in the bladder without catheterisation. *New Engl. J. Med.*, **259**, 337–339.

DELAERE, K.P., MICHIELS, H.G.E., DEBRUYNE, F.M.J. & MOONEN, W.A. (1977). Flavoxate hydrochloride in the treatment of detrusor instability. *Urol. Int.*, **32**, 377–381.

DOWNIE, J.W. & AWAD, S.A. (1976). Role of neurogenic factors in canine urethral wall tension and urinary continence. *Invest. Urol.*, **14**, 143–147.

DRAPER, J.E. & ZORGNIOTTI, A.W. (1954). The effects of banthine and similar agents on the urinary tract. *N.Y. State J. Med.*, **54**, 77–83.

DRUTZ, H.P., SHAPIRO, B.J. & MANDEL, F. (1978). Do static cystourethrograms have a role in the investigation of female incontinence? *Am. J. Obstet. Gynecol.*, **130**, 516–520.

EK, A. (1978). Adrenergic innervation and adrenergic mechanisms. A study of the human urethra. *Acta pharmac. tox.*, **43**, 35–40.

EK, A., ALM, P., ANDERSSON, K.E. & PERSSON, C.G.A. (1977). Adrenoceptor and cholinoceptor responses of the isolated human urethra. *Scand. J. Urol. Nephrol.*, **11**, 97–102.

ENHÖRNING, G. (1961). Simultaneous recording of intravesical and intra-urethral pressure. A study on urethral closure in normal and stress incontinent women. *Acta Chir. Scand., Suppl.* **276**, 1–68.

FINKBEINER, A.E., BISSADA, N.K. & WELCH, L.T. (1977). Uropharmacology: V. Choline esters and other parasympathomimetic drugs. *Urology*, **10**, 83–89.

FISCHER, C.R., DIOKNO, A. & LAPIDES, J. (1978). The anticholinergic effects of dicyclomide hydrochloride in uninhibited neurogenic bladder dysfunction. *J. Urol.*, **120**, 328–329.

FLETCHER, T.F. & BRADLEY, W.E. (1978). Neuroanatomy of the bladder-urethra. *J. Urol.*, **119**, 153–160.

FREWEN, W. (1979). Role of bladder training in the treatment of the unstable bladder in the female. *Urol. Clin. North Am.*, **6**, 273–277.

FROST, J.K. (1974). Gynecologic and obstetric cytopathology. In *Gynecologic and obstetric pathology*, 7th edition, eds. Novak, E.R. & Woodruff, J.D., pp 634–728. Philadelphia: Saunders.

GLEASON, D.M., BOTTACCINI, M.R. & DRACH, G.W. (1976). Urodynamics. *J. Urol.*, **115**, 356–361.

GLEASON, D.M., REILLY, R.J., BOTTACCINI, M.R. & PIERCE, M.J. (1974). The urethral continence zone and its relation to stress incontinence. *J. Urol.*, **112**, 81–88.

GLEN, E.S. & ROWAN, D. (1973). Continuous flow cystometry and urethral pressure profile measurement with monitored intravesical pressure: a diagnostic and prognostic investigation. *Urologic Research*, **1**, 97–100.

GOSLING, J.A., DIXON, J.S. & LENDRON, R.G. (1977). The autonomic innervation of the human male and female bladder neck and proximal urethra. *J. Urol.*, **118**, 302–305.

GOSLING, J. (1979). The structure of the bladder and urethra in relation to function. *Urol. Clin. North Am.*, **6**, 31–38.

GUARINO, J.R. (1981). Auscultatory percussion of the bladder to detect urinary retention. *New Engl. J. Med.*, **305**, 701.

HACHEN, H.J. & KRUCKER, V. (1977). Clinical and laboratory assessment of the efficacy of baclofen (Lioresal) on urethral sphincter spasticity in patients with traumatic paraplegia. *Eur. Urol.*, **3**, 237–240.

HEBJØRN, S. & WALTER, S. (1978). Treatment of female incontinence with emepronium bromide. Detrusor hyperreflexia in multiple sclerosis and urge incontinence in postmenopausal women, treated with emepronium bromide (Cetiprin). *Urol. Int.*, **33**, 120–129.

HOLMES, J.H. (1967). Ultrasonic studies of the bladder. *J. Urol.*, **97**, 654–663.

INTERNATIONAL CONTINENCE SOCIETY COMMITTEE ON STANDARDIZATION OF TERMINOLOGY (1981). Standardization of terminology of lower urinary tract function. Fourth report: Neuromuscular dysfunction. *Urology*, **17**, 618–620.

JAMES, E.D., FLACK, F.C., CALDWELL, K.P.S. & MARTIN, M.R. (1971). Continuous measurement of urine loss and frequency in incontinent patients. Preliminary report. *Br. J. Urol.*, **43**, 233–237.

JONAS, U. & HOHENFELLNER, R. (1978). A new concept of urodynamic evaluation of the lower urinary tract. *Urol. Int.*, **33**, 27–30.

JONAS, D., KRITTEN, J., ROSE, D. & WEBER, W. (1979). Residual urine determination in cysto-uroflow metering by electronic evaluation of volume differences. *Urol. Res.*, **7**, 265–268.

JÖNSSON, G. & ZEDERFELDT, B. (1957). A study of Cetiprin as a urologic drug. *Urol. Int.*, **4**, 293–305.

KANEKO, S., MINAMI, K., YACHIKU, S. & KURITA, T. (1980). Bladder neck dysfunction: the effect of alpha-adrenergic blocking agent phentolamine on bladder neck dysfunction and a fluorescent histochemical study of bladder neck smooth muscle. *Invest. Urol.*, **18**, 212–218.

KHANNA, O.P., DeGREGORIO, G.J., SAMPLE, R.G. & McMICHAEL, R.F. (1977). Histamine receptors in urethro-vesical smooth muscle. *Urology*, **10**, 378–381.

KLUGO, R.C. & CERNY, J. (1978). Standard water cystometry and electromyography of the external urethral sphincter. *Clin. Obstet. Gynecol.*, **21**, 669–678.

KONDO, A., KOBAYASHI, M., OTANI, T., TAKITA, T. & NARITA, H. (1980). Supersensitivity to prostaglandin in chronic neurogenic bladders. *Br. J. Urol.*, **52**, 290–294.

KOYANAGI, T. (1980). Studies on the sphincteric system located distally in the urethra: the external urethral sphincter revisted. *J. Urol.*, **124**, 400–406.

LAPIDES, J., HODGSON, N.B., BOYD, R.E., SHOOK, E.L. & LICHTWARDT, J.R. (1958). Pharmacologic reactions of the bladder. *J. Urol.*, **79**, 707–713.

LIPSCHULTZ, L.I., ROHNER, T.J., CURRY, T.H., RAEZER, D.M. & SCHOENBERG, H.W. (1973). The effect of imipramine on *in vitro* dog bladder muscle contractility. *Invest. Urol.*, **11**, 182–185.

LONGRIGG, J.N. (1982). Methods in Clinical Pharmacology: The upper urinary tract. *Br. J. clin. Pharmac.*, **13**, 461–468.

MADESBACHER, H. (1977). Combined pressure flow, EMG, and X Ray studies for the evaluation of neurogenic bladder disturbance: technique. *Urol. Int.*, **32**, 176–183.

McGUIRE, E.J. (1977). Combined radiographic and manometric assessment of urethral sphincter function. *J. Urol.*, **118**, 632–635.

MEISELS, A. (1967). The maturation value. *Acta Cytologica*, **11**, 249.

MERRILL, D.C., BRADLEY, W.E. & MARKLAND, C. (1971). Air cystometry 1. Technique and definition of terms. *J. Urol.*, **106**, 678–681.

MONTAGUE, D.K. & STEWART, B.H. (1979). Urethral pressure profiles before and after Ornade administration in patients with stress urinary incontinence. *J. Urol.*, **122**, 198–199.

MULROW, P.J., HUVOS, A. & BUCHANAN, D.L. (1961). Measurement of residual urine with ^{131}I labelled Diodrast. *J. lab. clin. Med.*, **57**, 109–113.

NORLÉN, L. & SUNDIN, T. (1978). Alpha-adrenolytic treatment in patients with autonomous bladders. *Acta pharmac. tox.*, **43**, 31–34.

ÖBRINK, A. & BUNNE, G. (1978). Treatment of urgency by instillation of emepronium bromide in the urinary bladder. *Scand. J. Urol. Nephrol.*, **12**, 215–218.

PARSONS, K.F. & TURTON, M.B. (1980). Urethral supersensitivity and occult urethral neuropathy. *Br. J. Urol.*, **52**, 131–137.

PEDERSEN, E., BJARNSON, E.V. & HANSEN, P-H. (1973). Treatment of neurogenic disorders of bladder function with flavoxate. *Saertryk as Ugeskr. Laeg.*, **135**, 2313–2317.

RAZ, S., CAINE, M. & ZEIGLER, M. (1972). The vascular component in the production of intraurethral pressure. *J. Urol.*, **108**, 93–96.

RITCH, A.E., GEORGE, C.F., CASTLEDEN, C.M. & HALL, M.R.P. (1977). A second look at emepronium bromide in urinary incontinence. *Lancet*, **i**, 504–506.

SALMON, U.J., WALTER, R.I. & GEIST, S.H. (1941). The use of estrogens in the treatment of dysuria and incontinence in postmenopausal women. *Am. J. Obst. Gynec.*, **42**, 845–851.

SETNIKAR, I., RAVASI, M.T. & DA RE, P. (1960). Pharmacological properties of piperidinoethyl-3-methyl-flavone-8-carboxylate hydrochloride, a smooth muscle relaxant. *J. Pharmac. exp.. Ther.*, **130**, 356–363.

SHAND, D.G., MacKENZIE, J.C., CATTELL, W.R. & CATO, J. (1968). Estimation of residual urine volume with ^{131}I-hippuran. *Br. J. Urol.*, **40**, 196–201.

SIGG, E.B. (1959). Pharmacological studies with tofranil. *Canad. Psychiat. Ass. J.*, **4** (suppl), 75–85.

SJÖSTRAND, S.E., SJÖGREN, C., & SCHMITERLÖW, C.G. (1972). Response of the rabbit and cat urinary bladders *in situ* to drugs and to nerve stimulation. *Acta pharmac. tox.*, **31**, 241–254.

SMITH, P.H., COOK, J.B. & PRASAD, E.W.M. (1974). The effect of Ubretid on bladder function after recent spinal cord injury. *Br. J. Urol.*, **46**, 187–192.

SUNDIN, T., DAHLSTRÖM, A., NORLÉN, L. & SVEDMYR, N. (1977). The sympathetic innervation and adrenoceptor function of the human lower urinary tract in the normal state and after parasympathetic denervation. *Invest. Urol.*, **14**, 322–328.

SUTHERST, J., BROWN, M. & SHAWER, M. (1981). Assessing the severity of urinary incontinence in women by weighing perineal pads. *Lancet*, **i**, 1128–1130.

TANAGHO, E.A. (1979). Membrane and microtransducer catheters: their effectiveness for profilometry of the lower urinary tract. *Urol. Clin. North Am.*, **6**, 110–119.

TANAGHO, E.A. & JONAS, U. (1977). Membrane catheter: effective for recording pressure in the lower urinary tract. *Urology*, **10**, 173–176.

THOMAS, D. (1979). Clinical urodynamics in neurogenic bladder dysfunction. *Urol. Clin. North Am.*, **6**, 237–253.

THÜROFF, J.W., JONAS, U., FROHNEBERG, D., PETRI, E. & HOHENFELLNER, R. (1980). Telemetric urodynamic investigations in normal males. *Urol. Int.*, **35**, 427–434.

TORRENS, M. & ABRAMS, P. (1979). Cystometry. *Urol. Clin. North Am.*, **6**, 79–85.

TSCHOLL, R. & LENZI, A. (1977). Recording of vesical pressure by means of CO_2-perfusion. *Br. J. Urol.*, **49**, 531–535.

TURNER, R.K. (1973). Conditioning treatment of nocturnal enuresis: present status. In *Bladder control and enuresis*, eds. Kolvin, I., MacKeith, R.C. & Meadow, S.R., pp. 195–210. Spastics International Medical Publications. London: Heinemann.

ULMSTEN, U. & ANDERSSON, K.E. (1977). The effects of emeprone on intravesical and intraurethral pressure in women with urgency incontinence. *Scand. J. Urol. Nephrol.*, **11**, 103–109.

ULMSTEN, U., ASMUSSEN, M. & LINDSTRÖM, K. (1977). A new technique for simultaneous urethrocystometry including measurements of the urethral pressure profile. *Urol. Int.*, **32**, 127–136.

VEATCH, W.M. (1980). The urethral chain: a simplified approach to chain cystourethrography. *Radiology*, **134**, 241–242.

WACHTEL, E.G. (1969). *Exfoliative cytology in gynaecological practice.* (2nd Edition) pp. 64, 65. London: Butterworths.

WALSH, J.B. & MILLS, G.L. (1981). Measurement of urinary incontinence in elderly incontinent patients. A simple and accurate method. *Lancet*, **i**, 1130–1131.

WARRELL, D.W., WATSON, B.W. & SHELLEY, P. (1963). Intravesical pressure measurement in women during movement using a radio-pill and an air probe. *J. Obstet. Gynaec. Br. Comm.*, **70**, 959–967.

WARWICK, R.T. (1979). The evaluation of urodynamic function. *Urol. Clin. North Am.*, **6**, 51–54.

WEIN, A.J. (1981). Classification of neurogenic voiding dysfunction. *J. Urol.*, **125**, 605–609.

WEIN, A.J., MALLOY, T.R., SHOFER, F. & RAEZER, D.M. (1980a). The effects of bethanechol chloride on urodynamic parameters in normal women and in women with significant residual urine volumes. *J. Urol.*, **124**, 397–399.

WEIN, A.J., RAEZER, D.M. & MALLOY, T.R. (1980b). Failure of the bethanechol supersensitivity test to predict improved voiding after subcutaneous bethanechol administration. *J. Urol.*, **123**, 202–203.

WILSON, P.D., AL SAMARRAI, M.T., BROWN, A.D.G. (1980). Quantifying female incontinence with particular reference to the Urilos system. *Urol Int.*, **35**, 298–302.